Updates on the use of inhaled corticosteroids in asthma

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Purpose of review

The purpose of this review is to compare and contrast the newer inhaled corticosteroid (ICS) ciclesonide with older ICSs in terms of pharmacodynamic and pharmacokinetic properties and how these affect comparative efficacy. In addition, clinical dosing strategies for ICSs including as-needed use will be explored.

Recent findings

Ciclesonide has demonstrated similar efficacy to that of fluticasone propionate and mometasone furoate in equipotent doses with a potentially improved therapeutic index. Once-daily administration of ICSs is generally not as effective as twice-daily. Continuous administration of ICSs does not change the natural history of asthma in either children or adults. Long-term administration of medium dose ICSs does not increase the risk of cataracts or osteopenia in children and young adults. Studies of as-needed ICSs in mild persistent asthma in adults and children have demonstrated mixed results, with some showing equal efficacy to continuous therapy and others showing superiority of continuous therapy.

Summary

Ciclesonide provides a newer ICS with favorable pharmacokinetics that may improve the therapeutic index, but assessment of its systemic effects such as growth await further studies. Continuous administration of ICSs in low to medium dose over many years is well tolerated. The use of as-needed ICSs in patients with mild persistent asthma is promising as a potential step-down therapy but awaits further studies.

Keywords

ciclesonide, dosing, fluticasone propionate, inhaled corticosteroids, mometasone furoate

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Introduction

Corticosteroids are the most effective antiinflammatories available to treat asthma [1]. Inhaled corticosteroid (ICS) monotherapy is more effective than any other long-term controller monotherapy for improving asthma control by improving impairment (symptoms, lung function, and bronchial hyperresponsiveness) and reducing risk (asthma exacerbations) [1]. The ICSs are the only long-term controllers associated with a reduction in the risk of dying from asthma [2]. Pharmacologic actions useful in treating asthma include increasing the number of β_2-adrenergic receptors and improving the receptor responsiveness to β_2-adrenergic stimulation, reducing mucus production and hypersecretion, reducing bronchial hyperresponsiveness, reducing the number of mucosal mast cells, enhancing eosinophil apoptosis, and reducing airway edema and exudation [3,4]. The glucocorticoid receptor is found in the cytoplasm of most cells throughout the body, explaining the multiple effects of systemic corticosteroids. Although there is no difference between glucocorticoid receptors found throughout the body, genetic differences between glucocorticoid receptors from different individuals may determine some of the variations in response [5].

The principal advantage of the ICSs is their high topical potency to reduce inflammation in the lung and low systemic activity [6–8]. The ICSs have high anti-inflammatory potency, approximately 1000-fold greater than endogenous cortisol, and differ from each other by as much as four-fold to six-fold [7]. However, potency differences can be overcome simply by giving different microgram dosages of drug. When administered in high doses, the ICSs can produce considerable systemic activity and adverse effects, so the pharmaceutical industry has continued to develop newer entities to improve their therapeutic index (ratio of topical activity to systemic activity) [6]. It is the purpose of this article to review the more recent pharmacodynamic aspects of the

currently available ICSs including dose–response relationships, pharmacokinetics, delivery devices, dosing frequency, and causes of relative resistance.

Dose–response

Comparable doses for the ICSs, beclomethasone dipropionate (BDP), budesonide (BUD), fluticasone propionate, mometasone furoate, and the newly released ciclesonide (CIC) are provided in Table 1. Most evidence is consistent with log-linear dose–response curves for both indirect and direct responses [6–8]. The log-linear nature of the dose–response curve raises the issue of how much of a difference in dose (or lung delivery) or potency is detectable. The measures used to assess efficacy [lung function, bronchial hyperresponsiveness (BHR), symptoms, and as-needed short-acting inhaled β_2-agonist use] are downstream events from the anti-inflammatory activity [7,8]. Therefore, investigators have begun using more direct measures of airway inflammation such as reactivity to inhaled adenosine monophosphate, fraction of exhaled nitric oxide (FeNO), exhaled breath condensate (EBC), and induced sputum eosinophils [9–13]. However, the relationship with changes in these parameters and improvement in lung function, symptoms, and risk for exacerbations is still not clearly delineated [1]. In general, it takes a four-fold difference in potency or dose to detect clinically significant differences in efficacy in comparative clinical trials [7,8,14–23,24••]. Table 1 showing comparable doses is based on extensive clinical trial data [1,8,16]. Clinically comparable doses take into consideration drug potency differences as well as device delivery differences.

Aerosol delivery of the preparations is remarkably variable, ranging from 10 to 60% of the nominal dose [i.e. that dose that leaves an actuator for a metered-dose inhaler (MDI) or, in the case of a dry-powder inhaler (DPI), that which is released on actuation of the inhaler] [7,8,15]. Different devices for the same chemical entity may result in two-fold differences in delivery, such as with fluticasone propionate and BUD MDIs and DPIs, or as much as eight-fold with BDP MDI chlorofluorocarbon and hydrofluoroalkane preparations [15]. Thus, the delivery method can make a significant difference in the relative comparable dose [1,8]. Although the last chlorofluorocarbon-propelled MDI-containing flunisolide will be manufactured by 30 June 2011, significant differences in delivery will still exist between the various hydrofluoroalkane-based MDIs depending on whether the drugs are soluble (BDP and CIC) or not (fluticasone propionate) in hydrofluoroalkane. Finally, the use of valved, holding-chambers (VHCs) can alter delivery from ICS MDIs [25]. This is unlikely to alter the relative efficacy unless the device is being used for patients unable to coordinate inhalation and actuation of the MDI because the differences in delivery between MDI and MDI + VHC are two-fold or less [6]. Adding a VHC to a small particle generating MDI such as hydrofluoroalkane-propelled BDP or CIC may lower or not change delivery [8,26,27•].

Key points

- Ciclesonide has demonstrated similar efficacy to that of fluticasone proprionate and mometasone furoate in equipotent doses with a potentially improved therapeutic index.
- Continuous administration of inhaled corticosteroids (ICSs) does not change the natural history of asthma in either children or adults.
- It is not clear that targeted therapy with small particle ICS metered-dose inhalers (MDIs) improves outcomes or even small airways disease over standard ICS MDIs and dry-powder inhalers.
- Long-term administration of medium dose ICSs does not increase the risk of cataracts or osteopenia in children and young adults.

Therapeutic index

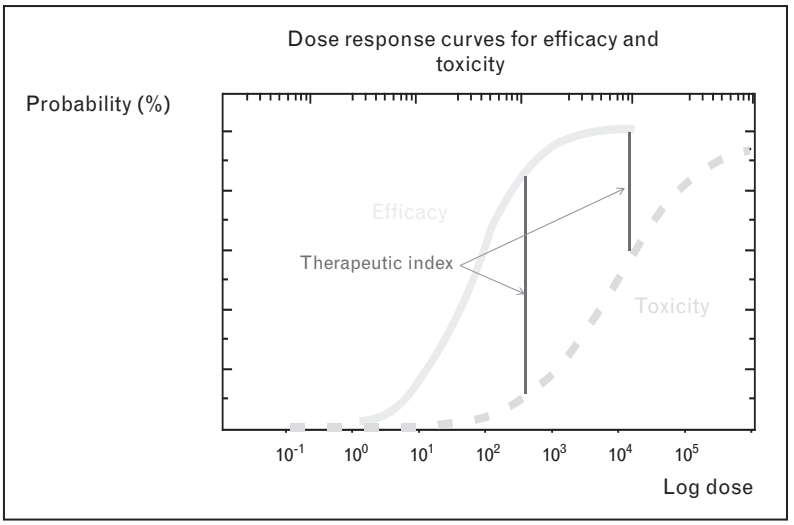
As corticosteroids do not preferentially stimulate lung glucocorticoid receptors, pharmacokinetic properties to decrease systemic exposure and maintain active drug in

Table 1 Comparative daily dosages (μg) of inhaled corticosteroids

	Low daily dose child[a]/adult	Medium daily dose child[a]/adult	High daily dose child[a]/adult
BDP			
HFA MDI	80–160/80–240	>160–320/>240–480	>320/>480
BUD			
DPI	180–360/180–540	>360720/>540–1080	>720/>1080
Nebules	500/UK	1000/UK	2000/UK
CIC, HFA MDI	80–160/160–320	>160–320/>320–640	>320/>640
FP			
HFA MDI	88–176/88–264	176–352/264–440	>352/>440
DPIs	100–200/100–300	200–400/300–500	>400/>500
MF, DPI	110/220	220–440/440	>440/>440

BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; DPI, dry-powder inhaler; FP, fluticasone propionate; HFA, hydrofluoroalkane; MDI, metered-dose inhaler; MF, mometasone furoate.
[a] 5–11 years of age except for BUD Nebules, which is 2–11 years.

Figure 1 Log dose–response curves for efficacy and systemic activity for an inhaled corticosteroid illustrating that as the dose increases the efficacy curve flattens and the therapeutic index narrows



the lung tissue are required to enhance the therapeutic index of the various ICSs [6–8]. Newer ICSs have been developed to improve the therapeutic index, but as can be seen with the dose–response curves in Fig. 1, the therapeutic index narrows as the dose is increased for any of the ICSs. Thus, the minimal effective dose to control asthma in the patient is always a goal of ICS therapy. Pharmacokinetic properties that have been established to enhance topical selectivity include rapid systemic clearance, poor oral bioavailability, and long residence time in the lung [6–8]. The systemic clearance of the available ICSs is very rapid, approaching the rate of liver blood flow with the exception of BDP and CIC and their active metabolites that are inactivated by blood esterases as well as liver metabolism (Table 2) [7,8]. The ICSs do differ in their oral bioavailability. They all undergo extensive first-pass metabolism from cytochrome P450 3A4 (CYP3A4) in both the gastrointestinal wall and the liver to less active substances with the exception of BDP, which is converted to the more active metabolite of 17-beclomethasone monopropionate (17-BMP), which is 40% bioavailable. This likely explains the lower therapeutic index for BDP compared with some of the newer ICSs (CIC, fluticasone propionate, and mometasone furoate) [6,23,28–30]. Of the three newest ICS (CIC, fluticasone propionate, and mometasone furoate), CIC has the more optimal pharmacokinetic profile for an enhanced therapeutic index [7,8]. This has resulted in an apparently improved therapeutic index for CIC over fluticasone propionate in preliminary studies [31,32], whereas mometasone furoate and fluticasone propionate, with similar pharmacodynamic/pharmacokinetic profiles, show a similar therapeutic index [33].

Table 2 Pharmacodynamic/pharmacokinetic variables of the inhaled corticosteroids[a]

ICS	Binding affinity[b]	Systemic clearance (l/h)	Half-life[c] (h)	Oral bioavailability (%)	Lung delivery (%)
BDP	13.5	120	2.7	40	50–60
BUD	9.4	84	2.8	11	
DPI					15–30
Nebules					5–8
CIC	12	228	3.4	<1	50
FP MDI	18	66	7.8	≤1	20
DPI					15
MF	23	53	5.0	<1	11

BDP, beclomethasone dipropionate; BUD, budesonide; CIC, ciclesonide; DPI, dry-powder inhaler; FP, fluticasone propionate; ICS, inhaled corticosteroid; MDI, metered-dose inhaler; MF, mometasone furoate.
[a] The values assigned BDP and CIC are for their active metabolites beclomethasone monopropionate and desciclesonide, respectively. Data compiled from [7,8] and the respective approved product information.
[b] Receptor binding affinities of ICS relative to dexamethasone equal to 1.
[c] Serum half-life following intravenous administration.

The ICSs produce dose-dependent systemic effects from a combination of the orally absorbed fraction and the fraction absorbed from the lung [1,6]. The fraction that reaches the lung is all absorbed systemically; thus, a slow absorption from the lung that results in an apparent long elimination half-life following aerosol administration (Table 2) enhances topical selectivity by lowering the peak systemic concentrations achieved [7,8]. The therapeutic index can be improved for high oral bioavailability ICSs by using a VHC device with the MDI, as they can reduce the oral dose by 80% [25]. However, the use of VHCs also can increase systemic activity by increasing lung delivery of drugs not absorbed significantly orally [6]. If this increase in lung deposition is two-fold or less, it will increase systemic activity without producing a clinically important increase in efficacy, thus decreasing the therapeutic index [6,8]. The effect of delivery device

is illustrated by fluticasone propionate, which had both the greatest therapeutic index when administered by DPI and the lowest therapeutic index when administered by MDI + VHC [28]. Mouth rinsing and spitting also will reduce the oral availability and may be particularly useful for DPI devices [1,25].

Systemic adverse effects can occur with any of the ICSs given in a sufficiently high dose. Long-term adverse effects of greatest concern include growth suppression in children, osteoporosis, cataracts, dermal thinning, and adrenal insufficiency and crisis [6]. Growth retardation occurs with low to medium doses depending on the ICS and delivery system [29,30,34–40]. The velocity is reduced in the first 6 months to 1 year of therapy and then returns to normal [29]. The effect is generally small (1–2 cm total) and not cumulative and although there has been no evidence of 'catch-up' growth, current studies suggest that attainment of predicted adult height is not affected [29,39,40]. It has been hypothesized that the children will continue to grow for a longer time [40]. The suppression of the hypothalamic–pituitary–adrenal axis, osteoporosis, cataract formation, and dermal thinning with bruising are dose dependent and do not appear except at high daily doses [6]. Recent evidence suggests that reduced bone mineral accretion in children resulting in osteopenia is more likely to result from two or more bursts of oral corticosteroids per year than from daily medium-dose ICSs [41,42]. Therefore, using ICSs in medium doses that decrease the risk of severe asthma exacerbations should reduce the risk of systemic corticosteroid-induced osteopenia [29,42]. However, adults with other risk factors (i.e. postmenopausal women) experience an increased risk of fractures on high-dose ICSs [43]. Although high daily dose ICSs has been associated with an increased risk of cataracts in high-risk adults [44], a recent long-term study [45•] (median 12 years) in children and young adults reported no cumulative dose-dependent risk of cataracts with medium-dose ICS therapy.

Drug interactions can reduce the therapeutic index of the ICSs by increasing their oral bioavailability and decreasing their systemic clearance. The ICSs (BDP, BUD, CIC, fluticasone propionate, and mometasone furoate) are metabolized in the gastrointestinal tract and liver by CYP 3A4 isoenzymes [8]. Potent inhibitors of CYP 3A4 such as ritonavir, itraconazole, and ketoconazole have resulted in increased systemic concentrations of these ICSs, and in some cases produce clinically significant Cushing syndrome and secondary adrenal insufficiency [46,47].

Clinical use issues

The response to ICSs is somewhat delayed. Most patients' symptoms will improve in the first 1–2 weeks of therapy and will reach maximum improvement in 4–8 weeks. Lung function improvement begins in 1–2 weeks and usually plateaus at 4 weeks but may increase slightly thereafter for 6–8 weeks [12,14,15, 20,30,48–51]. Improvement in bronchial hyperresponsiveness requires 2–3 weeks and approaches maximum in 1–3 months but may continue to improve over 1 year [13,29,31,48,51]. Most of the improvement in these parameters occurs at low to medium doses, and there is a large variability in response, with 10–20% of patients not demonstrating an improvement in either lung function or bronchial hyperresponsiveness [48,52]. Patients whose lung functions do not respond are not necessarily the same patients whose bronchial hyperresponsiveness does not improve [52]. Maximum decrease in FeNO occurs within 1 week and returns to baseline levels within 1–2 weeks following discontinuation [11,13,51]. Sensitivity to exercise challenge decreases after 4 weeks of therapy [53,54]. This effect is likely a result of reduction of mucosal and submucosal mast cells, as acute administration of single doses of ICSs prior to exercise have no effect [48]. Although the intensity of the responses can be dose dependent, the onset and offset of responses are not, nor do they differ significantly by which ICS is used.

Treatment with ICSs has failed to prevent the development of asthma in infants at high risk for developing asthma [38,55]. Long-term treatment with ICS in both adults and children failed to induce remission of asthma [29,39,56]. The effect of ICSs on loss of lung function over time has been inconsistent, with a positive benefit in some studies [57] but not all [58].

Not all patients with asthma will demonstrate a positive response to ICSs and some will experience a diminished response compared with population mean responses. Phenotypic factors that have been reported to result in a decreased response to ICS therapy include current or past smoking (even children exposed to smoke *in utero* exhibit a diminished response to ICS therapy), obesity, and vitamin D deficiency [59–63,64•]. However, it is important to note that although smoking and obesity result in a diminished response to ICSs, they are still more effective than leukotriene receptor antagonists in those conditions [65,66]. Tantisira *et al.* [67] recently demonstrated that three haplotype variants of the corticotrophin-releasing hormone receptor 1 were associated with an enhanced response to ICSs that was confirmed in three different asthma populations. Phenotypic characteristics that predict a favorable response to ICSs include bronchodilator reversibility, forced expiratory volume in one second (FEV_1), higher FeNO, higher total eosinophils, high sputum eosinophils, higher IgE, increased responsiveness to methacholine bronchoprovocation, and specifically in children a family history of asthma [68–70]. Short-term improvement in

lung function (FEV_1) over 6 weeks predicts long-term improvement in asthma control from ICS therapy [68]. So, although clinicians do not treat lung function, it is a strong predictor of success from therapy. Unfortunately, children often do not present with abnormal lung function or may be too young (<5 years old) to perform adequate lung function tests, so the therapeutic trial would have to be based upon symptoms. In addition, the clinician should continue to remember that nonadherence and incorrect inhalation technique are major causes of difficult asthma and apparent corticosteroid resistance [71–73]. Over 80% of patients referred to a difficult asthma clinic admitted poor adherence to inhaled controller therapy, including both ICS monotherapy and ICSs combined with long-acting inhaled β_2 agonists, with 35% filling 50% or fewer prescriptions [71]. In a large study [73] of over 4000 patients visiting general practitioners, 71% misused their MDIs. The patients with misuse were significantly more likely to have unstable asthma than proficient users. Even in clinical trials with encouragement and routine monitoring, adherence substantially decreases over time. An 18-month study [74] of BUD by DPI in 118 children 5–10 years old reported a fall from 86% adherence in the first 45 days to 59% in the last 45 days.

Dosing strategies

In the past it has been recommended that patients be started on medium to high doses of ICSs until control is achieved and then step down to the lowest dose that maintains control. However, that strategy is not supported by the literature, as starting patients at low doses, provided it is sufficient to produce an effect, results in similar onset of improvement and overall outcomes [75]. The current guidelines recommend starting patients on dosages based upon level of severity and then to titrate up or down based upon responsiveness to therapy [1]. This is a very reasonable approach, although most parallel dose-ranging trials in children and adults with mild-to-moderate persistent asthma show little to no differences between low and medium doses of ICSs [12,14,15,17–20,24••,49,50,76]. The one study to date that used attainment of well controlled or complete control status as defined by the asthma guidelines and gave escalating doses of ICSs to achieve control was the GOAL study [77], a 1-year trial in 3421 patients that compared escalating doses of fluticasone propionate 200, 500, and 1000 μg daily administered twice a day to escalating doses of fluticasone propionate combined with salmeterol. In the mild persistent and moderate persistent asthma stratum 70 and 60% cumulative patients were able to reach well controlled status on fluticasone propionate monotherapy. More telling is that in those who attained well controlled status, a majority (57%) in the mild persistent stratum gained control on the lowest dose of fluticasone propionate, whereas in the moderate persistent group only 33% gained control on the lowest dose, but the majority (66%) gained control at the medium dose. In both strata, increasing the fluticasone propionate dose to the highest level added only a further 10–15% of patients gaining control. Thus, starting patients at level of severity is likely to improve outcome from the therapy. It also confirms that step-up therapy is a viable alternative to add-on therapy in some patients.

There has been speculation that the newer small particle generating (or ultrafine particle) ICS MDIs may provide enhanced control because of their improved delivery to the peripheral small airways [78]. Although it has been well documented that small airways (<2 mm diameter) inflammation results in increased air-trapping and bronchial hyperresponsiveness and is associated with increased nocturnal asthma and severe asthma phenotype, it is not clear that targeted therapy with small particle ICS MDIs improves outcomes or even small airways disease over standard ICS MDIs and DPIs [15,79,80].

Many patients with mild persistent asthma can be effectively treated with once-daily ICS therapy, usually more effective given in the evening [81–86]. Currently, mometasone furoate is the only ICS with approved US Food and Drug Administration labeling to begin therapy once daily and BUD has once-daily approved labeling for patients once control is established on twice-daily dosing. All other ICSs are labeled for twice-daily dosing. No apparent specific pharmacologic or pharmacokinetic aspect of the ICSs allows once-daily dosing because all the agents studied (both the older low-potency and newer high-potency ICSs) have been effective, provided that patients had relatively mild-to-moderate asthma [8,54,80–83]. The newest ICS, CIC, is used in Europe on a once-daily basis in adults and children, but only has a twice-daily approved indication in adults in the United States. The US pivotal trials for CIC in children 4–11 years old with moderate-to-severe asthma gave once-daily dosing of 40, 80, and 160 μg. Although one trial demonstrated efficacy over placebo, one did not provide sufficient measures of efficacy to gain approval. A publication that combined the two trials demonstrated a statistical significant but clinically questionable improvement in FEV_1 of only 2.9 and 3.5% for the two higher doses [85]. Most patients with moderate disease can be controlled with twice-daily dosing of the ICSs [1,8,77]. Regardless of baseline severity, in patients who become well controlled on twice-daily ICSs, reduction to once daily can often maintain control. However, the clinician should remember that it has not been established that once-daily administration significantly improves adherence [86].

Conclusion

There is increasing interest for using, as needed, ICS therapy for deterioration of asthma to prevent severe

exacerbations requiring oral corticosteroids or urgent care visits [87–91,92••]. Some of this is based upon the approval of the BUD/formoterol combination for both maintenance and reliever therapy in Europe and other countries [87]. The studies have taken two forms: using the ICS and short-acting inhaled β_2 agonist together as an as-needed rescue therapy [88,91,92••] or using a short course (5–10 days) of high-dose ICS at an early sign of asthma deterioration and the short-acting inhaled β_2 agonist as needed [89,90]. So far the results have been mixed with the as-needed combination being superior to as-needed short-acting inhaled β_2 agonists alone [88,91,92••] and equivalent to the regular administration of ICS in some but not all outcomes. This may be due to the populations being studied. The two studies in adults with mild persistent asthma [88,89] reported no differences in exacerbations requiring oral corticosteroids, but greater improvement in the impairment domain (symptoms, asthma control days) and direct and indirect measures of airway inflammation (i.e. FeNO, bronchial hyperresponsiveness, and sputum eosinophils) [89] for daily continuous ICSs. However, the two studies in children reported significant reductions in exacerbations for continuous treatment compared with as-needed short-acting inhaled β_2 agonist only [92••], but not as-needed ICS or a significant difference in exacerbations favoring continuous ICS over as-needed ICS [91]. Neither of these studies showed an advantage for continuous ICS in measures of impairment (lung function or asthma control days). Of interest, both of these studies showed a decrease in growth velocity with continuous ICS compared with as-needed ICS or no ICS, indicating a greater safety margin with as-needed therapy. Thus, the clinician needs to weigh the benefit and risks of these different approaches in patients with mild persistent asthma.

References and recommended reading

Papers of particular interest, published within annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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